FIGURE 1

Human G Protein Coupled Receptor Family

(Receptors known as of January, 1999)

CLASS	LIGAND	NUMBER	TISSUE	PHYSIOLOGY	THERAPEUTICS
•Class I					
Rhodopsin like					
	•Amine				
	•Acetylcholine				
	(muscarinic & nicotinic)	5	Brain, Nerves, Heart	Neurotransmitter	Acuity, Alzheimer's
	•Adrenoceptors				
	•Alpha Adrenoceptors	6	Brain, Kidney, Lung	Gluconeogenesis	Diabetes, Cardiovascular
	•Beta Adrenoceptors	3	Kidney, Heart	Muscle Contraction	Cardiovascular, Respiratory
	•Dopamine	5	Brain, Kidney, GI	Neurotransmitter	Cardiovascular, Parkinson's
	•Histamine	2	Vascular, Heart, Brain	Vascular Permeability	Anti-inflammatory, Ulcers
	•Serotonin (5-HT)	16	Most Tissues	Neurotransmitter	Depression, Insomnia, Analgesic
	• Peptide				
	•Angiotensin	2	Vascular, Liver, Kidney	Vasoconstriction	Cardiovascular, Endocrine
	•Bradykinin	1	Liver, Blood	Vasodilation,	Anti-inflammatory, Asthma
	•C5a anaphylatoxin	1	Blood	Immune System	Anti-inflammatory
	•Fmet-leu-phe	3	Blood	Chemoattractant	Anti-inflammatory
	•Interleukin-8	1	Blood	Chemoattractant	Anti-inflammatory
	•Chemokine	6	Blood	Chemoattractant	Anti-inflammatory
	•Orexin	2	Brain	Fat Metabolism	Obesity
	•Nociceptin	1	Brain	Bronchodilator, Pain	Airway Diseases, Anesthetic
	•CCK (Gastrin)	2	Gastrointestinal	Motility, Fat Absorption	Gastrointestinal, Obesity, Parkinson's
	•Endothelin	2	Heart, Bronchus, Brain	Muscle Contraction	Cardiovascular, Respiratory
	•Melanocortin	5	Kidney, Brain	Metabolic Regulation	Anti-inflammatory, Analgesics
	•Neuropeptide Y	5	Nerves, Intestine, Blood	Neurotransmitter	Behavior, Memory, Cardiovascular
	•Neurotensin	1	Brain,	CNS	Cardiovascular, Analgesic
	•Opioid	3	Brain,	CNS	Depression, Analgesic
	•Somatostatin	5	Brain, Gastrointestinal	Neurotransmitter	Oncology, Alzheimer's
	•Tachykinin				
	(Substance P, NKA_1)	3	Brain Nerves	Neurohormone	Depression, Analgesic
	•Thrombin	3	Platelets, Blood Vessels	Coagulation	Anti-coagulant, Anti-inflammatory
	•Vasopressin-like	4	Arteries, Heart, Bladder	Water Balance	Anti-diuretic, Diabetic Complications
	•Galanin	1	Brain, Pancreas	Neurotransmitter	Analgesics, Alzheimer's
	•Hormone protein				
	•Follicle stimulating hormone	1	Ovary, Testis	Endocrine	Infertility
	•Lutropin-choriogonadotropic	1	Ovary, Testis	Endocrine	Infertility

•Thyrotropin	1	Thyroid	Endocrine	Thyroidism, Metabolism
•(Rhod)opsin				
•Opsin	5	Eye	Photoreception	Ophthalmic Diseases
•Olfactory	4(~1000)	Nose	Smell	Olfactory Diseases
•Prostanoid				
•Prostaglandin	5	Arterial, Gastrointestinal	Vasodilation, Pain	Cardiovascular, Analgesic
•Lysophosphatidic Acid	2	Vessels, Heart, Lung	Inflammation	Cancer, Anti-Inflammatory
•Sphingosine-1-phosphate	2	Most Cells	Cell proliferation	Cancer
•Leukotriene	1	White Blood Cells, Bronchus	Inflammation	Asthma, Rheumatoid Arthritis
•Prostacyclin	1	Arterial, Gastrointestinal	Platelet Regulation	Cardiovascular
•Thromboxane	1	Arterial, Bronchus	Vasoconstriction	Cardiovascular, Respiratory
•Nucleotide-like				
•Adenosine	4	Vascular, Bronchus	Multiple Effects	Cardiovascular, Respiratory
•Purinoceptors	4	Vascular, Platelets	Relaxes Muscle	Cardiovascular, Respiratory
•Cannabis	2	Brain	Sensory Perception	Analgesics, Memory
•Platelet activating factor	1	Most Peripheral Tissues	Inflammation	Anti-inflammatory, Anti-asthmatic
•Gonadotropin-releasing hormone like				
•Gonadotropin-releasing hormone	1	Reproductive Organs, Pituitary	Reproduction	Prostate Cancer, Endometriosis
•Thyrotropin-releasing hormone	1	Pituitary, Brain	Thyroid Regulation	Metabolic Regulation
•Growth hormone- inhibiting factor	1	Gastrointestinal	Neuroendocrine	Oncology, Alzheimer's
•Melatonin	1	Brain, Eye, Pituitary	Neuroendocrine	Regulation of Circadian Cycle
•Class II				
Secretin like				
•Secretin	1	Gastrointestinal, Heart	Digestion	Obesity, Gastrointestinal
•Calcitonin	1	Bone, Brain	Calcium Resorption	Osteoporosis
•Corticotropin releasing factor/urocortin	1	Adrenal, Vascular, Brain	Neuroendocrine	Stress, Mood, Obesity
•Gastric inhibitory peptide (GIP)	1	Adrenals, Fat Cells	Sugar/Fat Metabolism	Diabetes, Obesity
•Glucagon	1	Liver, Fat Cells, Heart	Gluconeogenesis	Cardiovascular
•Glucagon-like Peptide 1 (GLP-1)	1	Pancreas, Stomach, Lung	Gluconeogenesis	Cardiovascular, Diabetes, Obesity
•Growth hormone-releasing hormone	1	Brain	Neuroendocrine	Growth Regulation
•Parathyroid hormone	1	Bone, Kidney	Calcium Regulation	Osteoporosis
•PACAP	1	Brain, Pancreas, Adrenals	Metabolism	Metabolic Regulation
•Vasoactive intestinal polypeptide (VIP)	1	Gastrointestinal	Motility	Gastrointestinal
•ClassIII				
•Metabotropic Glutamate	7	Brain	Sensory Perception	Hearing, Vision
•$GABA_B$	1	Brain	Neurotransmitter	Mood Disorders
•Extracellular Calcium Sensing	1	Parathyroid, Kidney, GI Tract	Calcium Regulation	Cataracts, GI Tumors

Fig. 1, pg. 2

FIGURE 2

(a)
Wild-type DRY motif
D = may also be, preferably, E, L, P, Q, T, I, C, G, N, V, H, or A.
Y = may also be, preferably, W, F, S, I, Q, H, G, C, L, D, or A.
R = may also be, preferably, H, or C, or another amino acid, wherein GPCR is not constitutively desensitized

(b)
Modified DRY motif
2nd amino acid = any amino acid other than R or K, preferably A, D, E, N, and H.

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20210-91545.00F

FIGURE 3

The mutated amino acid at the second position of the DRY motif is underlined.

VASOPRESSIN V2 RECEPTOR - (Human)
accession P30518

R137H

```
  1 MLMASTTSAV PGHPSLPSLP SNSSQERPLD TRDPLLARAE LALLSIVFVA VALSNGLVLA
 61 ALARRGRRGH WAPIHVFIGH LCLADLAVAL FQVLPQLAWK ATDRFRGPDA LCRAVKYLQM
121 VGMYASSYMI LAMTLDHHRA ICRPMLAYRH GSGAHWNRPV LVAWAFSLLL SLPQLFIFAQ
181 RNVEGGSGVT DCWACFAEPW GRRTYVTWIA LMVFVAPTLG IAACQVLIFR EIHASLVPGP
241 SERPGGRRRG RRTGSPGEGA HVSAAVAKTV RMILVIVVVY VLCWAPFFLV QLWAAWDPEA
301 PLEGAPFVLL MLLASLNSCT NPWIYASFSS SVSSELRSLL CCARGRTPPS LGPQDESCTT
361 ASSSLAKDTS S
```

(SEQ ID NO:1)

ALPHA-1B ADRENERGIC RECEPTOR (ALPHA 1B-ADRENOCEPTOR).
(Golden hamster)
ACCESSION P18841
R143E

```
  1 MNPDLDTGHN TSAPAQWGEL KDANFTGPNQ TSSNSTLPQL DVTRAISVGL VLGAFILFAI
 61 VGNILVILSV ACNRHLRTPT NYFIVNLAIA DLLLSFTVLP FSATLEVLGY WVLGRIFCDI
121 WAAVDVLCCT ASILSLCAIS IDEYIGVRYS LQYPTLVTRR KAILALLSVW VLSTVISIGP
181 LLGWKEPAPN DDKECGVTEE PFYALFSSLG SFYIPLAVIL VMYCRVYIVA KRTTKNLEAG
241 VMKEMSNSKE LTLRIHSKNF HEDTLSSTKA KGHNPRSSIA VKLFKFSREK KAAKTLGIVV
301 GMFILCWLPF FIALPLGSLF STLKPPDAVF KVVFWLGYFN SCLNPIIYPC SSKEFKRAFM
361 RILGCQCRSG RRRRRRRLG ACAYTYRPWT RGGSLERSQS RKDSLDDSGS CMSGSQRTLP
421 SASPSPGYLG RGAQPPLELC AYPEWKSGAL LSLPEPPGRR GRLDSGPLFT FKLLGEPESP
481 GTEGDASNGG CDATTDLANG QPGFKSNMPL APGHF
```

(SEQ ID NO:2)

R143A

```
  1 MNPDLDTGHN TSAPAQWGEL KDANFTGPNQ TSSNSTLPQL DVTRAISVGL VLGAFILFAI
 61 VGNILVILSV ACNRHLRTPT NYFIVNLAIA DLLLSFTVLP FSATLEVLGY WVLGRIFCDI
121 WAAVDVLCCT ASILSLCAIS IDAYIGVRYS LQYPTLVTRR KAILALLSVW VLSTVISIGP
181 LLGWKEPAPN DDKECGVTEE PFYALFSSLG SFYIPLAVIL VMYCRVYIVA KRTTKNLEAG
241 VMKEMSNSKE LTLRIHSKNF HEDTLSSTKA KGHNPRSSIA VKLFKFSREK KAAKTLGIVV
301 GMFILCWLPF FIALPLGSLF STLKPPDAVF KVVFWLGYFN SCLNPIIYPC SSKEFKRAFM
361 RILGCQCRSG RRRRRRRLG ACAYTYRPWT RGGSLERSQS RKDSLDDSGS CMSGSQRTLP
421 SASPSPGYLG RGAQPPLELC AYPEWKSGAL LSLPEPPGRR GRLDSGPLFT FKLLGEPESP
481 GTEGDASNGG CDATTDLANG QPGFKSNMPL APGHF
```

(SEQ ID NO:3)

R143H

10345916 - 012202

```
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 61 VGNILVILSV ACNRHLRTPT NYFIVNLAIA DLLLSFTVLP FSATLEVLGY WVLGRIFCDI
121 WAAVDVLCCT ASILSLCAIS IDHYIGVRYS LQYPTLVTRR KAILALLSVW VLSTVISIGP
181 LLGWKEPAPN DDKECGVTEE PFYALFSSLG SFYIPLAVIL VMYCRVYIVA KRTTKNLEAG
241 VMKEMSNSKE LTLRIHSKNF HEDTLSSTKA KGHNPRSSIA VKLFKFSREK KAAKTLGIVV
301 GMFILCWLPF FIALPLGSLF STLKPPDAVF KVVFWLGYFN SCLNPIIYPC SSKEFKRAFM
361 RILGCQCRSG RRRRRRRRLG ACAYTYRPWT RGGSLERSQS RKDSLDDSGS CMSGSQRTLP
421 SASPSPGYLG RGAQPPLELC AYPEWKSGAL LSLPEPPGRR GRLDSGPLFT FKLLGEPESP
481 GTEGDASNGG CDATTDLANG QPGFKSNMPL APGHF
```

(SEQ ID NO:4)

R143N

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 61 VGNILVILSV ACNRHLRTPT NYFIVNLAIA DLLLSFTVLP FSATLEVLGY WVLGRIFCDI
121 WAAVDVLCCT ASILSLCAIS IDNYIGVRYS LQYPTLVTRR KAILALLSVW VLSTVISIGP
181 LLGWKEPAPN DDKECGVTEE PFYALFSSLG SFYIPLAVIL VMYCRVYIVA KRTTKNLEAG
241 VMKEMSNSKE LTLRIHSKNF HEDTLSSTKA KGHNPRSSIA VKLFKFSREK KAAKTLGIVV
301 GMFILCWLPF FIALPLGSLF STLKPPDAVF KVVFWLGYFN SCLNPIIYPC SSKEFKRAFM
361 RILGCQCRSG RRRRRRRRLG ACAYTYRPWT RGGSLERSQS RKDSLDDSGS CMSGSQRTLP
421 SASPSPGYLG RGAQPPLELC AYPEWKSGAL LSLPEPPGRR GRLDSGPLFT FKLLGEPESP
481 GTEGDASNGG CDATTDLANG QPGFKSNMPL APGHF
```

(SEQ ID NO:5)

angiotensin II receptor, type 1 (AT1A) [Rattus norvegicus].
ACCESSION NP_112247

R126H

```
      1 MALNSSAEDG IKRIQDDCPK AGRHSYIFVM IPTLYSIIFV VGIFGNSLVV
IVIYFYMKLK
     61 TVASVFLLNL ALADLCFLLT CPLWAVYTAM EYRWPFGNHL CKIASASVTF
NLYASVFLLT
    121 CLSIDHYLAI VHPMKSRLRR TMLVAKVTCI IIWLMAGLAS LPAVIHRNVY
FIENTNITVC
    181 AFHYESRNST LPIGLGLTKN ILGFLFPFLI ILTSYTLIWK ALKKAYEIQK
NKPRNDDIFR
    241 IIMAIVLFFF FSWVPHQIFT FLDVLIQLGV IHDCKISDIV DTAMPITICI
AYFNNCLNPL
    301 FYGFLGKKFK KYFLQLLKYI PPKAKSHSSL STKMSTLSYR PSDNMSSSAK
KPASCFEVE
```

(SEQ ID NO:6)

20222107519450A1

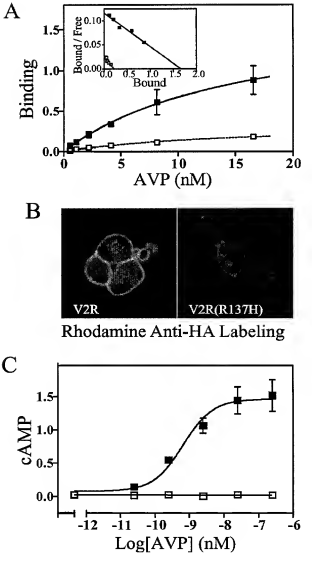
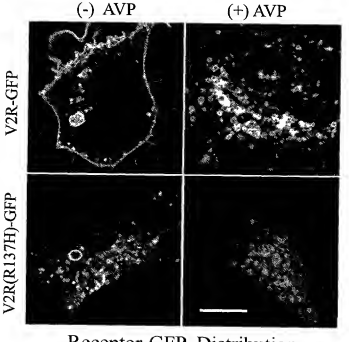


FIGURE 4

20220191945001



Receptor-GFP Distribution

FIGURE 5

20221019150107

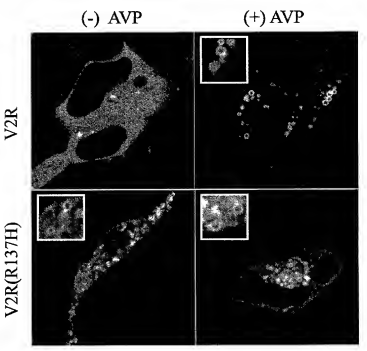


FIGURE 6

20020194650

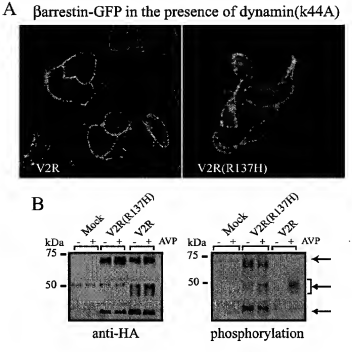


FIGURE 7

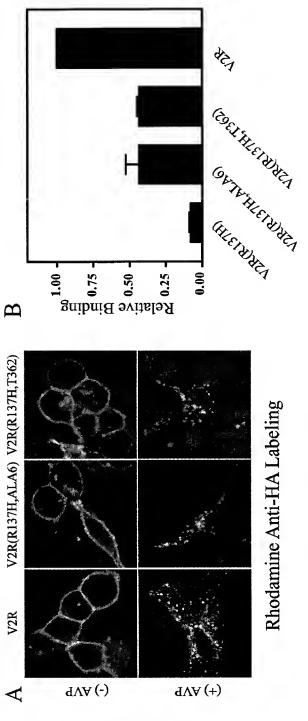

A
V2R
V2R(R137H,AL-A6)
V2R(R137H,T362)
(-) AVP
(+) AVP
Rhodamine Anti-HA Labeling
B
Relative Binding
0.00
0.25
0.50
0.75
1.00
V2R(R137H)
V2R(R137H,AL-A6)
V2R(R137H,T362)
V2R

FIGURE 8

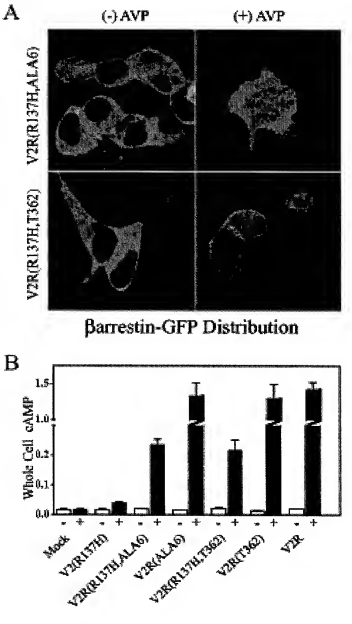

A
(-) AVP
(+) AVP
V2R(R137H,ALA6)
V2R(R137H,T362)
βarrestin-GFP Distribution
B
Whole Cell cAMP
1.5
1.0
0.2
0.1
0.0
- + - + - + - + - + - + - + - +
Mock
V2(R137H)
V2R(R137H,ALA6)
V2R(4ALA6)
V2R(R137H,T362)
V2R(T362)
V2R

FIGURE 9

20020119450 · 2002-08-15

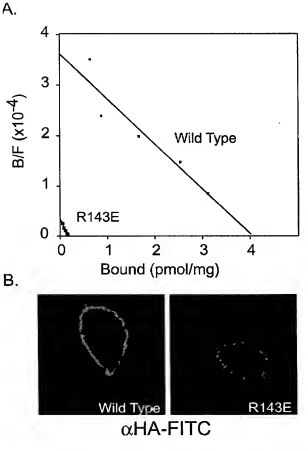


FIGURE 10

20020119450A1

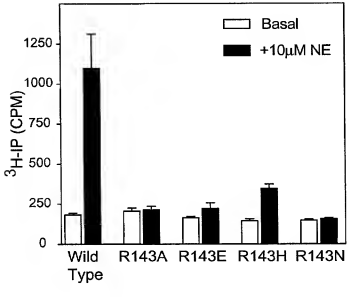
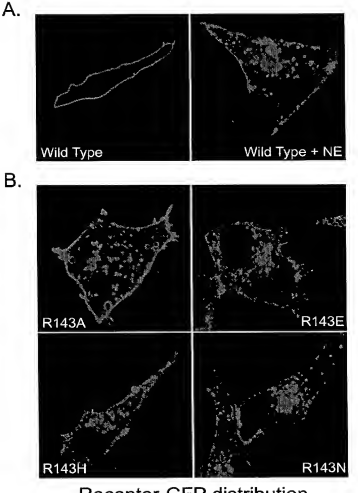


FIGURE 11



Receptor-GFP distribution

10054616-012202

FIGURE 12

10054616 012202

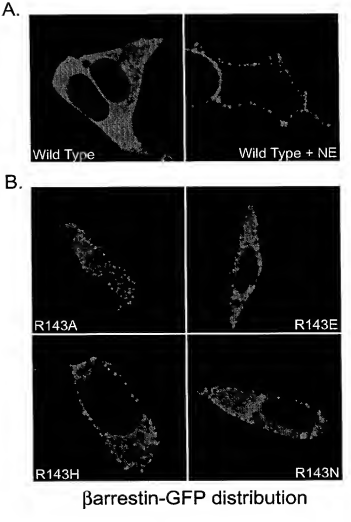


FIGURE 13

20221019194500T

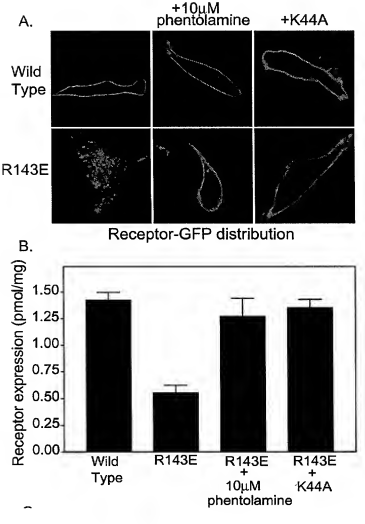
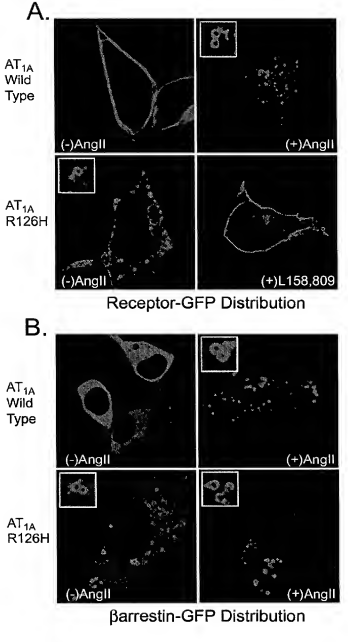


FIGURE 14



20220105154001

FIGURE 15

10054545 - 012202

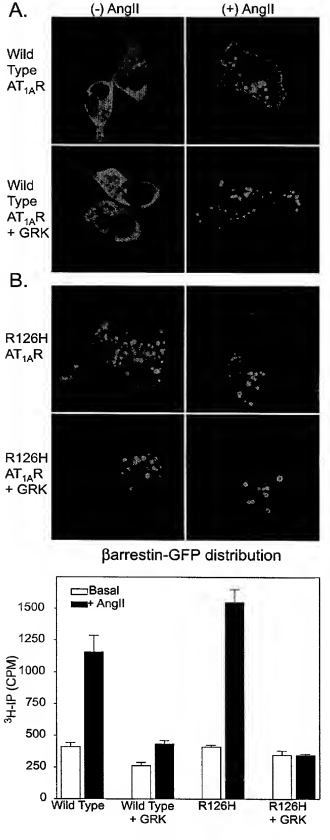


FIGURE 16

20020151945001

FIGURE 17

Homo sapiens arginine vasopressin receptor 2
ACCESSION NM_000054

R137H

```
atgct
6 catggcgtcc accacttccg ctgtgcctgg gcatccctct ctgcccagcc
tgcccagcaa
      66 cagcagccag gagaggccac tggacacccg ggacccgctg
ctagcccggg cggagctggc
     126 gctgctctcc atagtctttg tggctgtggc cctgagcaat
ggcctggtgc tggcggccct
     186 agctcggcgg ggccggcggg gccactgggc acccatacac
gtcttcattg gccacttgtg
     246 cctggccgac ctggccgtgg ctctgttcca agtgctgccc
cagctggcct ggaaggccac
     306 cgaccgcttc cgtgggccag atgccctgtg tcgggccgtg
aagtatctgc agatggtggg
     366 catgtatgcc tcctcctaca tgatcctggc catgacgctg
gaccaccacc gtgccatctg
     426 ccgtcccatg ctggcgtacc gccatggaag tggggctcac
tggaaccggc cggtgctagt
     486 ggcttgggcc ttctcgctcc ttctcagcct gccccagctc
ttcatcttcg cccagcgcaa
     546 cgtggaaggt ggcagcgggg tcactgactg ctgggcctgc
tttgcggagc cctggggccg
     606 tcgcacctat gtcacctgga ttgccctgat ggtgttcgtg
gcacctaccc tgggtatcgc
     666 cgcctgccag gtgctcatct tccgggagat tcatgccagt
ctggtgccag ggccatcaga
     726 gaggcctggg gggcgccgca ggggacgccg gacaggcagc
cccggtgagg gagcccacgt
    786 gtcagcagct gtggccaaga ctgtgaggat gacgctagtg
attgtggtcg tctatgtgct
    846 gtgctgggca cccttcttcc tggtgcagct gtgggccgcg
tgggacccgg aggcacctct
    906 ggaaggggcg ccctttgtgc tactcatgtt gctggccagc
ctcaacagct gcaccaaccc
    966 ctggatctat gcatctttca gcagcagcgt gtcctcagag
ctgcgaagct tgctctgctg
   1026 tgcccgggga cgcaccccac ccagcctggg tccccaagat
gagtcctgca ccaccgccag
   1086 ctcctccctg gccaaggaca cttcatcgtg a
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(SEQ ID NO:7)

20020194507

Syrian golden hamster alpha-1B adrenergic receptor mRNA
ACCESSION J04084

R143H

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      1 atgaat cccgatctgg acaccggcca caacacatca
gcacctgccc
     47 aatggggaga gttgaaagat gccaacttca ctggccccaa
ccagacctcg agcaactcca
    107 cactgcccca gctggacgtt accagggcca tctctgtggg
cctggtgctg ggcgccttca
    167 tcctctttgc cattgtgggc aacatcctgg tcatcctgtc
agtggcctgc aatcggcacc
    227 tgcggacgcc caccaactac ttcattgtca acctggccat
tgctgacctg ctgttgagtt
    287 tcacagtcct gcccttctcc gctaccctag aagtgcttgg
ctactgggtt ctggggcgca
    347 tcttctgtga catctgggca gcggtggacg tcctgtgctg
tacggcctcc atcctgagcc
    407 tatgtgccat ctccattgat cactacattg gggtgcgcta
ctctctgcag tacccactc
    467 tggtcacccg caggaaggcc atcttggcac tcctcagtgt
gtgggttttg tccacggtca
    527 tctccatcgg gcctctcctt ggatggaaag aaccagcgcc
caacgacgac aaggaatgcg
    587 gagtcaccga agaacccttc tatgccctct tttcctccct
gggctccttc tacatcccac
    647 tcgcggtcat tctggtcatg tactgccggg tctacatcgt
ggccaagagg accaccaaga
    707 acctggaggc tggagtcatg aaggagatgt ccaactccaa
ggagctgacc ctgaggatcc
    767 actccaagaa ctttcatgag gacaccctca gcagtaccaa
ggccaagggc cacaacccca
    827 ggagttccat agctgtcaaa ctttttaagt tctccaggga
aaagaaagca gccaaaacct
    887 tgggcattgt ggtcggaatg ttcatcttgt gttggctccc
cttcttcatc gctctcccac
    947 ttggctccct gttctccact ctcaagcccc cggacgccgt
gttcaaggtg gtattctggc
   1007 tgggctactt caacagctgc ctcaacccca tcatctaccc
gtgctccagc aaggagttca
   1067 agcgcgcctt catgcgtatc cttgggtgcc agtgccgtag
tggccgtcgc cgccgccgcc
   1127 gccgtcgtct gggcgcgtgc gcttacacct atcggccgtg
gacgcgcggc ggctcgctgg
   1187 agcgatcgca gtcgcggaag gactccctgg acgacagcgg
cagctgcatg agtggcagcc
   1247 agaggaccct gccctcggcg tcgcccagcc cgggctacct
gggtcgcgga gcgcagccac
   1307 cactggagct gtgcgcctac cccgaatgga aatccggggc
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tctgctcagt ctgccagagc
1367 ctccgggtcg ccgcggtcgc ctcgactctg ggcccctctt cactttcaag ctcttgggag
1427 agccggagag cccgggcacc gagggcgatg ccagcaatgg gggctgcgac gcaacgaccg
1487 acctggccaa tgggcagccc ggtttcaaga gcaacatgcc tctggcaccc gggcactttt
1547 ag
(SEQ ID NO:8)

R143A
1 atgaat cccgatctgg acaccggcca caacacatca gcacctgccc
47 aatggggaga gttgaaagat gccaacttca ctggccccaa ccagacctcg agcaactcca
107 cactgcccca gctggacgtt accagggcca tctctgtggg cctggtgctg ggcgccttca
167 tcctctttgc cattgtgggc aacatcctgg tcatcctgtc agtggcctgc aatcggcacc
227 tgcggacgcc caccaactac ttcattgtca acctggccat tgctgacctg ctgttgagtt
287 tcacagtcct gcccttctcc gctaccctag aagtgcttgg ctactgggtt ctggggcgca
347 tcttctgtga catctgggca gcggtggacg tcctgtgctg tacggcctcc atcctgagcc
407 tatgtgccat ctccattgat **gc**ctacattg ggtgcgcta ctctctgcag taccccactc
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647 tcgcggtcat tctggtcatg tactgccggg tctacatcgt ggccaagagg accaccaaga
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1547 ag
(SEQ ID NO:9)

R143E

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ggccaagggc cacaacccca

20020151550

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1547 ag

(SEQ ID NO:10)

R143N

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1427 agccggagag cccgggcacc gagggcgatg ccagcaatgg gggctgcgac gcaacgaccg
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1547 ag

(SEQ ID NO:11)

Rattus norvegicus Angiotensin II receptor, type 1 (AT1AR)
ACCESSION NM_030985

R126H

1 a tggcccttaa ctcttctgct gaagatggta tcaaaagaat
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102 ctacagcatc atctttgtgg tgggaatatt tggaaacagc ttggtggtga ttgtcattta
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222 cttatgcttt ttgctgactt gtcccctgtg ggcagtctat accgctatgg agtaccgctg

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(SEQ ID NO:12)

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